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Evidence-based surgical treatment of primary angle-closure glaucoma

Tratamento cirúrgico do glaucoma primário de ângulo fechado baseado em evidências

Tratamiento quirúrgico del glaucoma primario de ángulo cerrado basado en evidencias

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KEYWORDS

Glaucoma, Angle-Closure; Iridectomy; Lens, Crystalline; Cataract Extraction.

ABSTRACT

The review analyzed scientific evidence regarding the surgical treatment of patients with primary angle closure (PAC). The literature presents evidence indicating prophylactic laser peripheral iridotomy (LPI) for treating the contralateral eyes of patients with acute PAC (APAC) and eyes with symptoms of previous PAC; however, there is no data supporting its routine use in patients suspected with PAC (occludable angles). Research has reported the use of cataract surgery for treating eyes with APAC, immediately after the clinical management of the condition, and primary angle-closure glaucoma (PACG). Improved control of intraocular pressure (IOP) and reduction in the amount of hypotensive eye drops have been postoperatively observed. Compared with LPI, clear lens extraction was associated with greater reduction in IOP and in the amount of ocular hypotensive drug use as well as better quality of life and cost-effectiveness for eyes with PACG and PAC with IOP >30mmHg.

PALAVRAS-CHAVE

Glaucoma de Ângulo Fechado; Iridectomia; Cristalino; Extração de Catarata.

RESUMO

O objetivo da presente revisão é analisar as evidências científicas referentes ao tratamento cirúrgico de pacientes com fechamento angular primário (FAP). A iridectomia periférica a laser profilática (IPL) apresenta evidências na literatura para o tratamento de olhos contralaterais de pacientes com FAP agudo e olhos com sinais de FAP prévio, porém, não há respaldo científico para a sua realização rotineira em suspeitos de FAP (ângulos oclusíveis). A realização de cirurgia de catarata tem embasamento científico para tratamento de olhos com FAP agudo, imediatamente após controle clínico da crise, e GPAF, tendo sido observados melhor controle da pressão intraocular (Po) e redução da quantidade de colírios hipotensores oculares após a cirurgia. A extração do cristalino transparente, quando comparada com a IPL, apresentou maior redução da Po, redução do número de hipotensores oculares, melhor qualidade de vida e melhor custo-efetividade em olhos com GPAF e FAP com Po maior que 30mmHg.

PALABRAS CLAVE

Glaucoma de Ángulo Cerrado; Iridectomía; Cristalino; Extracción de Catarata.

RESUMEN

El objetivo de la presente revisión es analizar las evidencias científicas referentes al tratamiento quirúrgico de pacientes con cierre angular primario (CAP). La iridectomía periférica a láser profiláctica (IPL) presenta evidencias en la literatura para el tratamiento de ojos contralaterales de pacientes con CAP agudo y ojos con señales de CAP previo, sin embargo, no hay respaldo científico para su realización rutinaria en pacientes con sospechas de CAP (ángulos oclusivos). La realización de cirugía de catarata tiene base científica para tratamiento de ojos con CAP agudo, inmediatamente después del control clínico de la crisis, y GPAC, habiéndose observado mejor control de la presión intraocular (Po) y reducción de la cantidad de colirios hipotensores oculares post cirugía. La extracción del cristalino transparente, cuando comparada con a IPL, presentó mayor reducción de la Po, reducción del número de hipotensores oculares, mejor calidad de vida y mejor costo-efectividad en ojos con GPAC y CAP con Po mayor que 30mmHg.

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Primary angle-closure glaucoma (PACG) affects a large number of people worldwide and is associated with a high risk of blindness. A study published in 2006 estimated that the global number of patients with PACG would be 15.7 million in 2010 and 21 million in 2020, with 3.9 million with bilateral blindness in 2010 and 5.3 million in 2020. The same study estimated that women and Asians would represent approximately 70% and 47% of these cases.[1] The Glaucoma Project conducted in the southern region of Brazil examined 1,636 individuals and identified that the prevalence of PACG was 0.7%.[2] The Professor Nassim Calixto Glaucoma Service, based in Brazil, identified an incidence of 22.7 cases of acute primary angle closure (PAC) for each 1,000 visits.[3]

In 2002, in an attempt to standardize the nomenclature adopted in research, Foster et al. described a new PACG classification emphasizing anatomical and functional damages. Eyes were identified as primary angle-closure suspects (PACSs) when there was either appositional contact between the peripheral iris and posterior trabecular meshwork or an occludable angle: for epidemiological research, it was defined as an angle at which approximately 180° of the posterior trabecular meshwork (the most pigmented part) cannot be visualized. This is an arbitrary definition that has also been adopted in the Brazilian Society of Glaucoma's 2nd Consensus on Angle-closure Glaucoma. Longitudinal studies are warranted to better define this parameter. PAC has been defined as a condition in which eyes have occludable angles and features indicating trabecular obstruction by the peripheral iris, such as peripheral anterior synechiae (PAS), elevated intraocular pressure, distortion of the radially orientated iris fibers, *Glaukomflecken*, or excessive pigment deposition on the trabecular surface. However, according to this definition, in PAC, the optic disc should not have any evidence of glaucoma, i.e., of anatomic or functional glaucomatous damage. This classification is a great advancement and is extremely useful in research. Nonetheless, it has a few limitations. It does not consider or distinguish different types of damages to the trabecular meshwork and optic nerve, does not analyze the presence of symptoms, and disregards the importance of ocular hypertension in PAC.[4,5]

LASER PERIPHERAL IRIDOTOMY (LPI)

LPI is a non-invasive, low-cost, relatively safe outpatient procedure, which is normally used as prophylactic treatment in patients with PAC and has an efficacy comparable to surgical iridotomy.[6,7] However, it should be noted that it is not a risk-free procedure and may cause hyphema, anterior uveitis, PAS, cataract, corneal decompensation, and ciliochoroidal effusion.[8,9]

LPI is performed, usually using a *neodymium-doped yttrium aluminium garnet* (Nd:YAG) laser to prevent or alleviate pupillary block in patients with PAC. A relative pupillary block occurs when the aqueous humor flowing through the pupil is hindered by forces acting in the anterior segment that result in contact of the posterior surface of the iris and the anterior surface of the lens. As a result, the peripheral iris is bent forward and consequently causes the closure of the anterior-chamber angle.[10,11] Eyes with angle closure demonstrate important biometric differences from normal eyes, such as a smaller corneal diameter, shallow anterior chamber, thicker lens, more anterior position of the lens, and smaller axial diameter.[12] In these eyes, prophylactic LPI can avoid acute PAC (APAC) crises, reducing iris convexity[13,14], increasing angle opening[15], and mitigating pupillary block.[16] Moreover, we should consider that patent LPI does not mitigate angle closure and does not prevent the elevation of intraocular pressure (IOP) in plateau iris configuration.

LPI – SCIENTIFIC EVIDENCE

Prophylactic indication of LPI for contralateral eyes of patients with APAC (acute glaucoma)

The prophylactic use of LPI in contralateral eyes of patients with APAC is effective in preventing acute crises. IOP in contralateral eyes can increase in 12% of treated cases compared with 75% of untreated eyes.[17-20] LPI also prevents long-term increase in IOP in 88.8% of contralateral eyes.[19]

Indication of prophylactic LPI for eyes with PAC signs: pigment traces from the iris on the wall of the iridocorneal angle, elevation of IOP, goniosynechiae or atrophy of the iris, *Glaukomflecken* or distortion of the radial pattern of the iris

The prophylactic use of LPI in eyes with signs of previous PAC may help in the prevention of APAC, with a direct influence on the deepening of the anterior chamber.[16,20-22]

Prophylactic indication of LPI in eyes with occludable angles (PACS): no consensus in the literature

Despite the existence of previous population studies, the definition of occludable angle still lacks a clear scientific basis. The most widely adopted, practical definition is that it occurs when the posterior trabecular meshwork (pigmented portion) is not seen in gonioscopy through ≥180 degrees, without additional maneuvers, in the primary position of the gaze, when using a narrow slit, and after making sure that no light beam reaches the pupil to avoid opening the angle.[4,5]

For PACS, i.e., occludable angle, the literature fails to provide substantial support for the indication of prophylactic LPI and little is known about the natural history of these patients. In addition, there are few clinical trials comparing prophylactic LPI with a control group.[23-25] A population-based study conducted at the Zhongshan Ophthalmic Center, a specialized tertiary hospital in Guangzhou, China, screened 11,991 individuals and randomized patients with PACS in both eyes for undergoing LPI (n=889; prophylactic LPI) or not undergoing treatment (n=889; untreated).[26] After 72 months of follow-up, PAC was observed in 19 patients treated with LPI and in 36 untreated patients. Therefore, although prophylactic LPI had a modest effect on the prevention of PAC, owing to the low incidence of PAC, the indiscriminate use of prophylactic LPI is not recommended. Considering this, in patients with occludable angle, clinical observation of the iridocorneal angle with serial gonioscopy and IOP measurements is recommended.[27] The decision for prophylactic LPI can be based on important individual factors, such as the presence of symptoms, family history of glaucoma or blindness, the patient's inability to keep up with ophthalmologic follow-up, unfavorable socioeconomic conditions, and frequent need for pupillary dilation. The appearance of signs and symptoms in patients with angle closure identified by gonioscopic examination is an absolute indication of LPI.

A study examined the efficacy of LPI in PAC by researching the literature available in PubMed and Cochrane databases until August 2017[28] and analyzed 300 citations, followed by the selection of the 36 most relevant studies. The selected studies were classified into levels I, II, and III of scientific relevance. It was shown that LPI widens the anterior-chamber angle and has a good safety profile at all PAC stages. Most eyes that were identified as PACS did not receive any other intervention, while many eyes with PAC and APAC, as well as most of those with PACG, received further treatment. Progression to PACG is uncommon in eyes with PACS and PAC. Currently, data comparing the efficacy of LPI versus that of other treatments at different stages of angle closure are limited. One randomized clinical trial demonstrated that cataract surgery was superior to LPI in patients with APAC and another one demonstrated that clear lens extraction (CLE) was superior to LPI in patients with PACG and PAC with IOP >30mmHg.[28]

CATARACT SURGERY AND PAC

Role of lens in PAC

The most important features of PAC are that the eye has a shallow anterior chamber and a narrow angle. The average depth of the anterior chamber in PAC is approximately 1.8mm, which is 1mm less than that in the normal eye.[29,30] Angle closure is rare when the anterior-chamber depth exceeds 2.5mm.[31] Reduced anterior-chamber volume,[32,33] small corneal diameter,[34-36] and small axial diameter[34-36] are the characteristics of eyes with PAC. The most satisfactory explanation for the reduction in anterior-chamber depth is the increase in lens thickness and its progressive anterior positioning with aging.[29,36-38] The lens in eyes with PAC has larger axial diameter than that in normal eyes,[29,34,36,37] and thicker lenses are significantly more anterior.[36,37] Increase in lens thickness caused an estimated 0.35-mm reduction in anterior-chamber depth and a 0.65-mm anteriorization, resulting in a total 1-mm reduction in anterior-chamber depth compared with that in normal eyes.[29,36] The growth of the lens, with an increase in the number of lens fibers during adulthood, results in an increase in thickness and anterior curvature.[32] A new parameter called "lens vault," defined by the perpendicular distance between the anterior pole of the lens and a horizontal line that joins the scleral spurs, measured with horizontal OCT scans of the anterior segment (AS-OCT), was identified as a potential risk factor for PAC.[39]

Efficacy of lens removal in PAC

After lens extraction and foldable intraocular lens implantation in normal eyes, the iris diaphragm posteriorly shifts, the anterior chamber deepens approximately 850 microns, and the angle widens by 10

degrees. These clinical findings may be extremely important in patients with PAC.[40] Thus, cataract surgery may help eliminate one of the main etiological factors of pupillary block and thus effectively reduce intraocular pressure in patients with PAC.[41,42]

Considerations of the risk of cataract surgery in patients with occludable angles or PAC

Because of the biometric features previously described, cataract surgery in patients with occludable angles or PAC requires a careful approach. These patients usually exhibit shallow anterior chambers and more anterior lenses; some of them have PAS and hyporeactive pupils that exhibit reduced dilation. Special measures may be necessary during surgery, such as the pre- or perioperative intravenous use of mannitol, the use of iris retractors or maneuvers to improve perioperative mydriasis, and the use of specific parameters for phacoemulsification, in addition to considering pars plana vitrectomy for cases with a high risk of ciliary block glaucoma. Moreover, a smaller axial diameter and a more anterior lens can pose a challenge in the calculation of intraocular lenses. Thus, some cases require an experienced surgeon.[43,44]

CATARACT SURGERY AND PAC: SCIENTIFIC EVIDENCE

APAC treatment with early cataract surgery

APAC may cause immediate loss of vision if not promptly treated. In addition to treatment using ocular hypotensive drugs and anti-inflammatory eye drops, the usual treatment to reverse an acute glaucoma crisis involves oral acetazolamide and venous hyperosmolar solutions. After reduction in IOP and the alleviation of the immediate symptoms of APAC, the possibility of LPI can be evaluated. Moreover, in case of cataract, early phacoemulsification with intraocular lens implantation (PHACO + IOL) can be considered.[41,45] A few studies have analyzed the clinical treatment of patients with APAC for resolving crisis, and other randomized studies analyzed LPI and early PHACO + IOL (patients with cataract). Cataract surgery was reportedly more effective than LPI for preventing the subsequent elevation of IOP, and the number of ocular hypotensive drugs used was lower in the PHACO + IOL group with no difference in corneal endothelial cell count between the two groups.[41,45]

PACG treatment with early cataract surgery

A systematic review and meta-analysis assessed five randomized clinical trials and 11 controlled clinical trials (1,495 eyes) with the objective of comparing the efficacy and safety of trabeculectomy (TREC), phacotrabeculectomy with intraocular lens implantation (PHACOTREC + IOL) and PHACO + IOL in PACG.[46] PHACOTREC + IOL was found to be superior to TREC, which in turn was superior to PHACO + IOL, for reducing IOP. PHACOTREC + IOL and PHACO + IOL increased the depth of the anterior chamber more than TREC. These were similar with regard to visual acuity results, but PHACOTREC + IOL was superior to PHACO + IOL in ocular hypotensive drug reduction.[46]

Treatment of chronic PACG with CLE

One prospective randomized clinical trial compared TREC with the use of mitomycin C (MMC) and CLE in 50 eyes of 50 patients with chronic PACG without adequate drug control and without cataract, with a follow-up of 2 years.[47] Both TREC withmmC and CLE significantly reduced IOP, with no pronounced difference between the groups after 24 months: an 8.4-mmHg (or 34%) reduction using CLE versus an 8.9-mmHg (or 36%) reduction using TREC. TREC was more effective than CLE to reduce the dependence of antiglaucomatous eye drops; however, TREC was more associated with complications. In the TREC group, 33% of the eyes showed progression to cataract during follow-up.

PACG and PAC treatment with CLE

An important randomized clinical trial called EAGLE was conducted using a methodology designed to analyze the effectiveness of CLE with intraocular lens implantation for treating patients with PACG and PAC with IOP >30mmHg.[48]

The EAGLE study included patients from 30 eye hospitals in the Great Britain and four countries in East Asia. The inclusion criteria were as follows: patients aged >50 years, those with a recent diagnosis of PACG or PAC, those with an IOP >30mmHg, and those with a presence of a clear lens. The exclusion criteria were as follows: advanced glaucoma, previous diagnosis of acute angular closure, increased surgical risk (e.g., corneal opacity, Fuchs' endothelial dystrophy, pseudoexfoliation, and previous vitreoretinal

surgery), symptomatic cataract, any previous intraocular procedure or laser treatment, axial diameter ≤19.0mm, secondary angle-closure glaucoma, and the history of retinal ischemia, macular edema, or age-related macular degeneration.[48] A total of 419 individuals were included, 155 with PAC and 263 with PACG, one participant rabdomly assigned to CLE was classified as a crossover; moreover, 208 underwent CLE and 211 underwent LPI.

At the end of a 36-month follow-up, the CLE group, compared with the LPI group, had lower IOP (16.6±3.5mmHg vs. 17.9±4.1mmHg) and lower hypotensive eye drop use (0.4±0.8 versus 1.3±1.0), respectively. Furthermore, the European Quality of Life 5-Dimension questionnaire score of the CLE group was higher.[49] The cost-effectiveness of the method used in the EAGLE study was analyzed using a Markov model to extrapolate the results to 5 and 10 years.[50] CLE demonstrated a 67%-89% chance of being cost-effective in 3 years and could represent cost savings in 10 years.[50] Refractive results after CLE were also assessed in the EAGLE study, and the corrected visual acuity remained stable over 3 years.[51] The preoperative mean of the spherical equivalent was +1.7±2.4 and became +0.08±0.95 after 36 months. At the end of the follow-up, 59% and 85% of the eyes presented a ±0.5-diopter and a ±1-diopter difference from the predicted refraction, respectively, which was considered suboptimal.[51]

After the EAGLE study, some authors argued that there is scientific evidence for the change in conduct in clinical practice regarding the use of CLE as the primary treatment of angle closure.[52,53] However, these researchers also emphasized that such a paradigm shift could only be applied to patients who meet the EAGLE inclusion criteria, i.e., those with PACG or PAC and IOP >30mmHg.[52,53] Therefore, there is still no scientific support to extrapolate CLE to all PACS eyes (occludable angles).

In conclusion, the literature presents evidence indicating the use of prophylactic LPI for the treatment of contralateral eyes of patients with APAC and eyes with signs of previous PAC; however, there is no scientific evidence supporting its routine use in all PACSs (occludable angles). There is scientific base for the use of cataract surgery to treat eyes with APAC, immediately after the clinical management of the crisis, and to treat those with PACG with better IOP management and reduction in the amount of hypotensive eye drop use after surgery. Compared with LPI, CLE showed a greater reduction in IOP and in the amount of ocular hypotensive drug use, as well as better quality of life and cost-effectiveness, for eyes with PACG and PAC when IOP was >30mmHg.

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